



## PERSPECTIVES

# Scaling up of latent tuberculosis infection treatment for close contacts of tuberculosis in Taiwan

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In 2008, Taiwan started a national tuberculosis (TB) program to implement latent tuberculosis infection (LTBI) treatment for TB contacts. Child contacts aged younger than 13 years were the first priority group to receive

treatment. Countries in West-Pacific and South-Eastern Asia, such as Japan, Hong Kong, and South Korea have scaled up their LTBI strategies in recent years in order to reach the long-term goal of stopping TB.<sup>1–3</sup> Incidence of TB

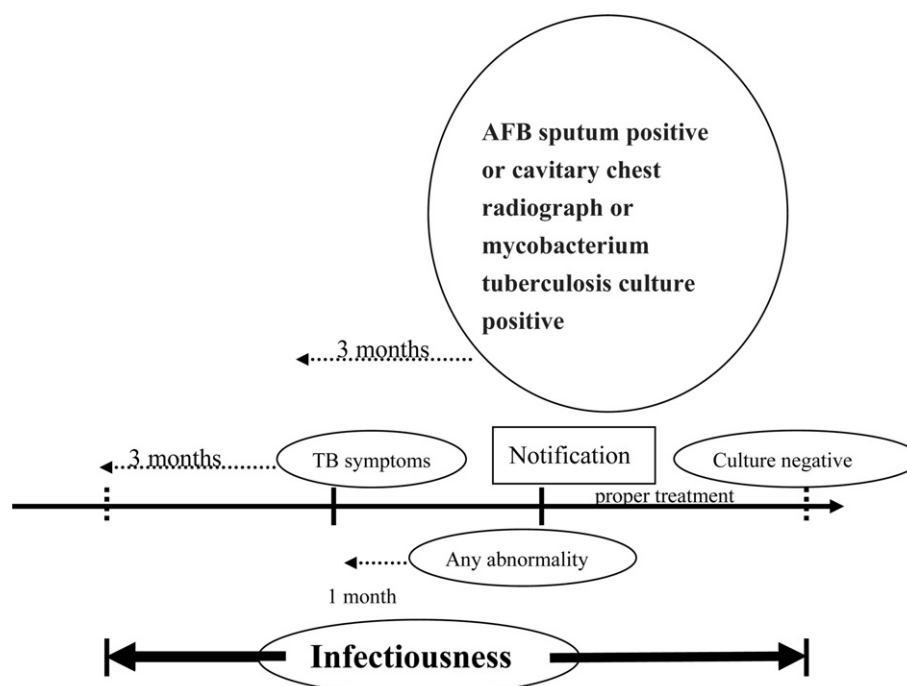
**Table 1** Definitions of the period of infectiousness in TB cases. (Guidelines for estimating the beginning of the period of infectiousness of persons with tuberculosis, by index case characteristic; revised and translated from Chapter 6, Manual for TB Control in Taiwan, <http://www.cdc.gov.tw/public/Attachment/04199462271.doc>).

Characteristic			Recommended minimum beginning of likely period of infectiousness
TB symptoms	AFB sputum positive	Cavitary chest radiograph or <i>Mycobacterium tuberculosis</i> culture positive	
Yes	Yes	Yes	3 mo before symptom onset or first positive finding consistent with TB disease, whichever is longer
No	Yes	Yes	3 mo before first positive finding consistent with TB
Yes	Yes	No	3 mo before symptom onset or first positive finding consistent with TB disease, whichever is longer
Yes	No	Yes	3 mo before symptom onset or first positive finding consistent with TB disease, whichever is longer
No	Yes	No	3 mo before first positive finding consistent with TB
No	No	Yes	3 mo before first positive finding consistent with TB
Yes	No	No	1 mo before symptom onset or first positive finding (e.g., abnormal chest radiograph) consistent with TB disease, whichever is longer
No	No	No	1 mo before date of suspected diagnosis

AFB = Acid-fast bacilli; TB = tuberculosis.

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**Figure 1** Illustration of how to estimate the beginning of the period of infectiousness of persons with tuberculosis, by index case characteristics. AFB = Acid-fast bacilli; TB = tuberculosis.

**Table 2** Examination schedule for TB contacts. (Revised and translated from Appendix 6-1 from Manual for TB Control in Taiwan, <http://www.cdc.gov.tw/public/Attachment/03111034771.doc>).

Timing/age/methods		Index condition/age <sup>a</sup>		
		Positive for either sputum AFB or culture, or cavitation on the chest radiograph (index cases aged 5 years and older <sup>a</sup> )	Negative for sputum AFB and culture, without cavitation on the chest radiograph (index cases aged 5 years and older <sup>a</sup> )	index cases aged <5 years <sup>a</sup> + extrapulmonary TB without lung involvement (all age index cases)
Within 1 month after TB diagnosis of index cases confirmed	CXR for contacts aged 13 years and older	○	○	○
The 3 <sup>rd</sup> month	CXR and TST for contacts aged <13 years	○	○ Note 1 <sup>b</sup> : CXR only, no need to do TST	○ Note 2: CXR only, no need to do TST
	2 <sup>nd</sup> TST for contacts aged <13 years who had negative result of 1 <sup>st</sup> TST	○	×	×
The 12 <sup>th</sup> month (±1 month)	2 <sup>nd</sup> CXR for contacts aged ≥13 years	○	×	×
	2 <sup>nd</sup> CXR for contacts aged <13 years	○ Note 3: the contacts with negative result of 2 <sup>nd</sup> TST can waive the 2 <sup>nd</sup> CXR if their index cases are regularly treated	× <sup>b</sup>	×

AFB = Acid-fast bacilli; CXR = chest radiograph; MDRTB = multi-drug resistance TB; TST = tuberculin skin test.

Special conditions:

1. Contacts for MDRTB cases: public health nurses should remind contacts to complete CXR before the end of the first month after notification of MDRTB; contacts should receive CXR every 6 months for 2 years.

2. Contacts for chronic TB cases: annual CXR.

3. If contacts are pregnant, sputum for AFB/mycobacterial culture will be checked if contacts can provide sputum. When pregnant contacts have respiratory symptoms, CXR could be performed to rule out active TB and avoid delay to diagnosis.

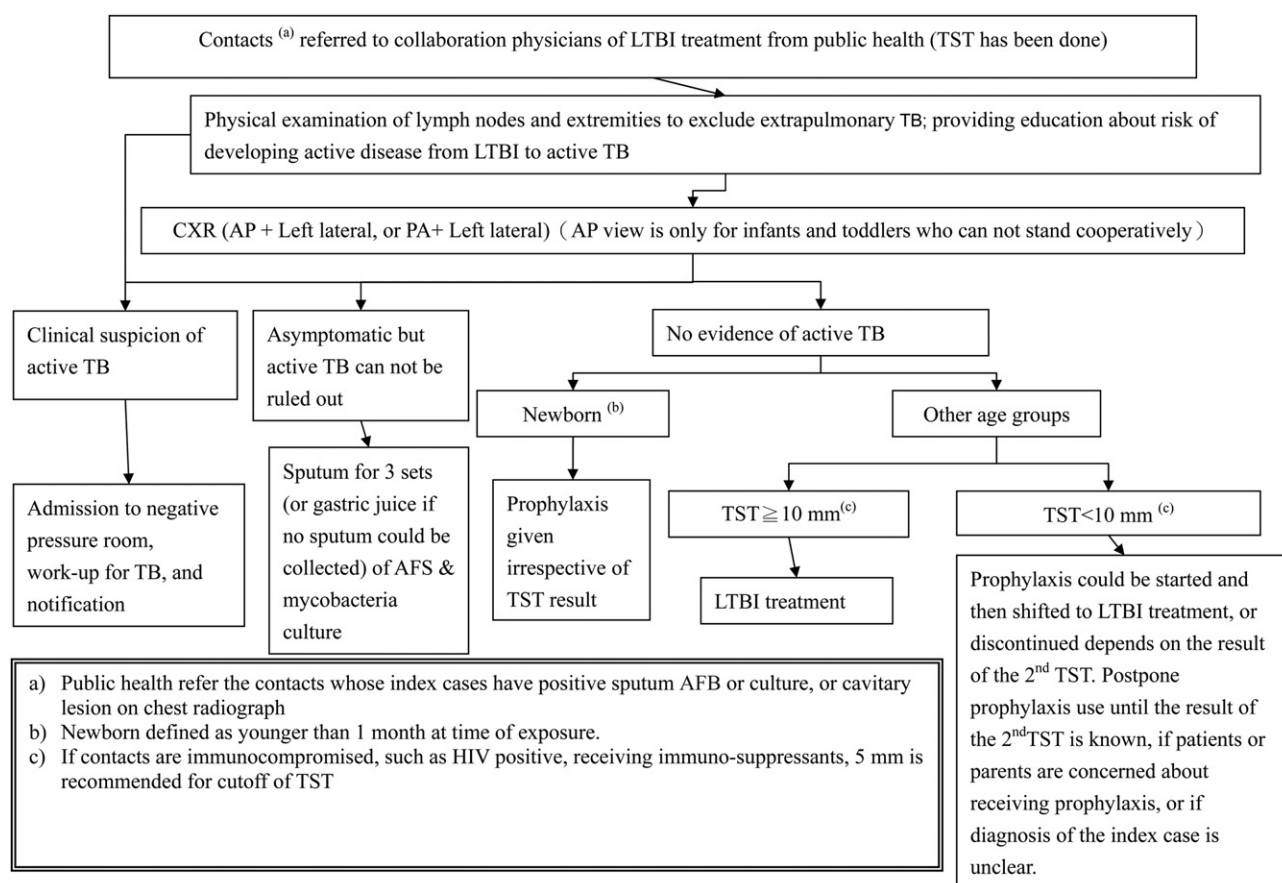
<sup>a</sup> Currently, age of index cases are not considered and there is no difference in contact investigation methods for their contacts. The recommended criteria for index cases will be implemented in 2012 as shown in this table.

<sup>b</sup> Currently, contacts <13 years, whose index cases with negative for sputum AFB and culture without cavitation on the chest radiograph received one TST within one month after TB diagnosis of index cases is confirmed. These contacts received only CXR at 1 year after last exposure to index case if they had positive result of TST. The recommended method for contact investigation will be implemented in 2012 as shown in this table.

in Taiwan decreased gradually from 73/100,000 in 2005 to 57/100,000 in 2010.<sup>4</sup> With decreasing TB case number, and decreasing mortality rate under the directly observed treatment (DOT) strategy, diagnosis and treatment of LTBI in high-risk populations has become the most important strategy for case management.

The sensitivity and specificity of the tuberculin skin test (TST) in identifying *Mycobacterium tuberculosis* (MTB) infection has been found to be less than optimal in a population with prior Bacillus Calmette-Guérin (BCG) vaccination, probably due to antigenic cross-reactivity between purified protein derivative from repeated or recent BCG and environmental mycobacteria.<sup>5</sup> In Taiwan, the BCG booster program for 6<sup>th</sup> grade students was stopped in 1997.<sup>6</sup> Therefore, young people who were born after January 1<sup>st</sup>, 1986 received only one BCG vaccination, at birth. As a result, the TST was still useful in identifying these adolescent and young adult contacts eligible for LTBI treatment in Taiwan. Several studies revealed that IFN- $\gamma$  release assays (IGRAs) could provide higher specificity than the TST in BCG-vaccinated populations. However, IGRAs could probably offer higher sensitivity than the TST in elderly or immunocompromised populations with waning or poor T cell response.<sup>7,8</sup>

Isoniazid monotherapy for LTBI treatment is still the standard drug of choice for LTBI treatment. A recently introduced alternative regimen for LTBI is 12 doses of once weekly rifapentine (900 mg) plus isoniazid (900 mg). Optimistic preliminary results were reported in adults with low prevalence of human immunodeficiency virus (HIV) infection who were randomized to receive 12 doses of rifapentine regimen and 9 months of isoniazid.<sup>9</sup> In a trial conducted in South Africa where the prevalence of TB was very high, all regimens including a 3-month course of intermittent rifapentine or rifampin with isoniazid, and continuous isoniazid were not superior to 6 months of isoniazid in HIV patients.<sup>10</sup> No resistance to rifampin was observed among the 58 strains collected in patients with active TB during the 4000 person-year follow-up. Patients in the continuous-isoniazid group had a 58% lower rate of TB or death than those receiving the 6-month control regimen of isoniazid, but the rates of TB in the continuous-isoniazid group markedly increased when therapy was discontinued. Shorter, intermittent, rifapentine-based LTBI treatment with a stringent DOT strategy could provide the most benefits when provided to patients in rural area where DOT is labor intensive and costly.



**Figure 2** The flow chart for latent tuberculosis infection treatment. (Revised and translated from appendix 14-2 from Manual for TB Control in Taiwan, <http://www.cdc.gov.tw/public/Attachment/03111034771.doc>). AP view = anteroposterior view; CXR = chest radiography; LTBI = latent tuberculosis infection; PA view = posteroanterior view; TB = tuberculosis; TST = tuberculin skin test. Data have been obtained from: Chapter 10, Taiwan Guidelines for TB Diagnosis and Treatment, 4th edition. <http://www.cdc.gov.tw/public/Attachment/132413462971.pdf>; Chapter 14, Manual for TB Control in Taiwan, <http://www.cdc.gov.tw/public/Attachment/0219495471.pdf>; Chapter 8, Taiwan Guidelines for TB Diagnosis and Treatment, 4th edition.

Table 1 shows how the period of infectiousness in TB cases can be determined by public health workers investigating TB contact in Taiwan. The beginning of the period of infectiousness of TB cases depends on four characteristics of the index TB patients: presenting symptoms of TB; positive for acid-fast bacilli in the sputum; findings of the chest radiograph; and positive for MTB culture. Fig. 1 illustrates the timeline for the start of infectiousness, TB symptoms, and abnormalities of either chest radiography or sputum examination. The end of infectiousness is on the day of submission of a sputum culture that later turns negative. Contacts are identified according to infectious period and a time of exposure to the index case of up to eight hours/day or an accumulative 40 hours. Public health nurses should start preliminary contact investigation after TB diagnosis of index cases is confirmed. Within 1 month, the index TB case should be interviewed, their contacts identified and TB screening provided to every identified contact according to the age and contagiousness of index cases and age of contacts (Table 2). Contacts of index cases with positive sputum and cavitation on the chest radiograph need evaluation and either 12-month follow-up or LTBI evaluation according to their age. Contacts receive only one chest radiograph without evaluation of LTBI if index cases are younger than 5 years (all forms), have extrapulmonary TB without lung involvement, or have negative sputum and no cavitation on the chest radiograph. The algorithm of diagnosis and treatment of LTBI is shown in Fig. 2.

In conclusion, it is the time to consider wider implementation of LTBI treatment in Taiwan, especially for adolescents with a history of close contact with infectious TB. The slogan of World TB Day in 2012 is "Stop TB in My Lifetime"; using the most cost-efficient strategy to identify LTBI cases and providing treatment through an effective delivery system may help Taiwan to contribute to a world free of TB.

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